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Recurrent Implantation Failure: History, Etiology, Advances and Ongoing Challenges

Sheron K George[1]

[1]Department of Biology T. John Pre-University College Bengaluru

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Abstract: Infertility is the inability to conceive even after unprotected intercourse for more than 12 months. In India, the prevalence of infertility has been growing to the extent that 10-15 percent of couples experience this condition. Recurrent implantation failure (RIF) is a complex medical condition in which implantation becomes unsuccessful despite the advancements in Assisted Reproductive Technologies (ART). We lack a clear understanding of the definition and standardisation of RIF protocols. The etiology behind RIF is multifactorial, comprising both maternal and embryonic factors. Maternal factors include endometrial abnormalities, environmental exposure, physical aspects, and dysregulation of the immune system. Chromosomal aberrations such as aneuploidy are embryo-born factors that impede implantation. The latest studies have shed light on the novel mechanisms of RIF. Recent research has identified miRNA that can hinder the implantation processes, opening the door to many more avenues for targeted therapies, gene knockdown, and immune modulation. This review is a comprehensive overview of the history, causes, advancements, and challenges related to RIF.

Keywords*: Recurrent Implantation Failure, Assisted Reproductive Technology, Endometrial Receptivity Assay, Infertility.*

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I. INTRODUCTION

Implantation is an intricate process in which a blastocyst attaches to the uterine wall. It occurs through three stages of apposition, adhesion and invasion. The blastocyst initially comes into contact with the uterine surface during adhesion. Apposition is the process during which the blastocyst more tightly aligns with the uterine lining, and invasion occurs when the blastocyst's trophoblastic cells penetrate the maternal endometrial tissue to facilitate the onset of a pregnancy. Disruption in any of these three phases can result in implantation failure. The two main indications of failed implantations are the absence of a gestational sac when viewed through ultrasonography and the lack of human chorionic gonadotrophin (hCG) spike in serum. Clinical studies have shown that a lack of the expected hCG increase, measured within 48 hours apart, is a reliable indication of non-viable pregnancies or failed implantation (Ma et al., 2023). About 10–15% of couples worldwide experience infertility, although assisted reproductive technologies are becoming more popular as a way to alleviate the psychological and physical burden. Recurrent Implantation Failure (RIF), which is defined as the inability to obtain a clinical pregnancy after three or more IVF cycles with high-quality embryos, continues to be a significant clinical issue even while the overall pregnancy success rates of IVF are advancing. The recent estimates suggest that 10–20% of women undergoing IVF treatment may suffer from RIF. The women having RIF are likely to have less successful rates of implantation even after multiple transfers, posing a serious concern (Mrozikiewicz et al., 2021).

RIF has no clarification, which is a complicated and multifaceted issue. It results from a confluence of numerous factors pertaining to the conditions of both the mother and the embryo. Maternal age is one such factor that governs the implantation rate, as the age progresses the incidence of chromosomal aberrations can be high. Uterine lining issues, structural anomalies including fibroids or polyps which accounts for 25 percent of RIF, and immunological factors that could influence embryo acceptance are important maternal factors. Furthermore, poor embryo quality and failure to implant can be linked to sperm DNA fragmentation. Chromosome abnormalities, such as aneuploidy, constitute some of the reasons that lead to implantation failure from the embryonic side(Garneau & Young, 2021). Historically, the assessment of endometrial receptivity was limited to the histological dating of the endometrium. The breakthroughs, such as the Endometrial Receptivity Assay (ERA), endometrial receptivity (ER) mapping, and the Window of Implantation (WOI) tests, aid in the extensive analysis of the transcriptomic profile of endometrium. Along with this, Artificial intelligence aids in the exquisite mastery of endometrial function (Bashiri et al., 2018a).

Still, numerous unsolved concerns persist regarding the complete etiology of RIF. Although appreciable progress has been made, deeper research is required to identify the specific biomarkers of endometrial receptivity, assess the effects of

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modest uterine defects, and elucidate the relation between sperm quality and embryo development. Furthermore, as it may affect the success of implantation, the involvement of the microbiome in the uterine environment is a new field that needs more clarification. Some studies show the link between Lactobacillus species and uterine pH and, consequently, successful implantation. However, some studies are unable to reveal this. In conclusion, a more thorough strategy is required to pinpoint and resolve the various root causes of recurrent implantation failure. This review is a brief account of the history and critical advances highlighting the complexity of its causes and the potential of new technologies to enhance treatment options.

II. EARLY INVESTIGATIONS ON RIF

Endometrium is an exceptional layer distinguished for its complexity, which makes it suitable for its selective function (Critchley et al., 2020). This layer is precise in its function to hold a seasoned blastocyst, also, it gets sloughed off in the truancy of fertilisation due to the interplay of paracrine and endocrine signalling (Fitzgerald et al., 2021). This organ is composed of a blend of glandular epithelial cells and stromal cells. In the 1950s, poor embryo quality and abnormalities in the mother's uterus were the main causes of RIF (N. Li et al., 2022). One of the significant works in recognizing the connection between the endometrium and embryo implantation was published in the 1950s by Noyes and Hertig (Kliman, 2020). By classifying the phases of the menstrual cycle and establishing the framework for determining endometrial receptivity towards an embryo, the creation of endometrial dating techniques began (Noyes et al., 1950).

In the early investigation, the uterine environment was examined for physical abnormalities such as adhesions, fibroids, polyps, or congenital deformities(Wei et al., 2023). The critical juncture was the comprehension that a debilitated endometrium could not host a successful embryo (Noyes et al., 2019). Endometrial histology dating was initiated during the late 1980s to ascertain the timing of endometrial receptivity (Lamb et al., 1972). Nonetheless, histological dating was biased and varied depending on the observer, hence, its utility has been interrogated (Coutifaris, 2004). Thereafter, researchers commenced to explore the concept of contemporizing embryo maturation, typically at the blastocyst stage, with the receptivity of the endometrium, which normally occurs 7 to 8 days after ovulation. Scientists were investigating RIF's molecular and immunological aspects by the 1990s (Lédée et al., 2016). Studies have shown that altered cytokine levels can hinder the process of implantation. Furthermore, the RIF prototype became more intricate due to genetic conditions like mosaic embryo formation and abnormal parental variants.

A significant development in early 2010 was the Endometrial Receptivity Assay (ERA). ERA examines endometrial gene expression to accurately determine the window of implantation (WOI) and estimate the optimal duration for embryo transfer, thus building a foundation for molecular diagnostics (Neykova et al., 2022). This understanding can further be enhanced by the rigorousness of machine learning and artificial intelligence (AI) algorithms for evaluating transcriptomic data. Currently, non-invasive techniques like gene editing and pre-genetic testing are emerging to enhance the rates of implantation (Tamura et al., 2023). Lately, the attention towards the correlation of endometrial microbiome and RIF is expanding(Gao et al., 2024). According to studies, the uterine microbiota can affect both embryo implantation and the receptive nature of the endometrium (Benner et al., 2018). Diagnostics using PGT and immune modulation are the developing strategies for sorting out this infertility issue.

- *Root Causes Contributing to Rif*

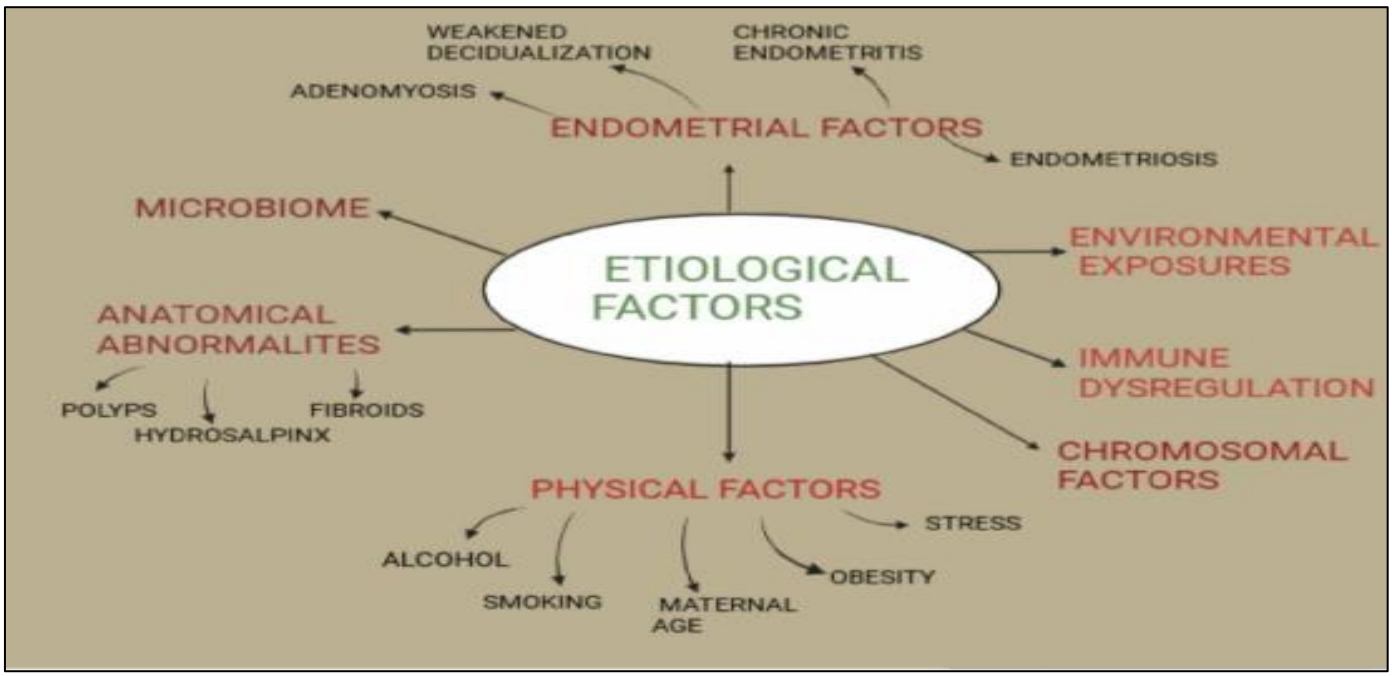

Fig 1 Etiological Factors of RIF

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➢ *Physical Determinants*

- *SMoking*

Smoking may impact embryo development and change endometrial receptivity. Smoking cigarettes has been associated with decreased endometrial blood flow, decreased estrogen synthesis, and elevated oxidative stress, all of which have a detrimental effect on implantation (Bashiri et al., 2018b). (Huang et al., 2017) showed that women with smoking habits are more prone to miscarriages and have less chances of implantation. In men, smoking causes sperm quality to decline, thereby increasing the chances of fragmentation in sperm DNA; a fragmentation rate beyond 10% can cause serious abnormalities. When the quality of oocytes and sperms are compromised, it leads to chromosomal anomalies like aneuploidy (Wilton et al., 2003).

- *Alcoholism*

Consuming alcohol negatively impacts ovarian function, endometrial growth, and hormonal equilibrium, thus hindering implantation (Benkhalifa et al., 2023). Further, it has been associated with an increase in inflammation and oxidative stress, both of which may impede embryonic development during the early stages of pregnancy. It can also cause dysregulation in the neurocognitive function. A study noted that women who consumed alcohol were more likely to experience implantation failure after IVF. The study found that alcohol interferes with the production of progesterone, a key hormone required for embryo implantation (Ricci et al., 2017).

- *Obesity*

Obesity is an important factor that affects one's fertility status. Studies have shown that in obese women, the markers of endometrial receptivity are altered (Schultze et al.,2015). Obesity can hinder the function of insulin production and may result in elevated levels of leptin, which eventually cause an imbalance in reproductive function. Women with low BMI may suffer from low estrogen levels, reduced number of antral follicles and the thickness of endometrium will be poor, leading to failure of successful implantation. On the other hand, women with a BMI of more than 30 Kg/m^2 have excessive fat deposition in their body, affecting their egg quality, thereby elevating the chances of PCOS (polycystic ovarian syndrome) and endometrial issues. Oriento et al.,2008 showed that obese patients have lower pregnancy rates.

- *Stress*

Stress is another factor leading to recurrent implantation failure (Catherino, 2011). Stress can result in altered cortisol levels, which is a hormone associated with the fight or flight response. Chronic stress can result in high cortisol levels that result in diminished secretion of estrogen and progesterone, which are essential for ovulation, implantation and successful pregnancy. In accordance with a study, women who have reported high levels of stress had reduced blood flow in their uterine tissue, which may negatively impact the endometrial lining, thus rendering it less responsive to a fertilized embryo. This is because stress triggers the sympathetic nervous system, which narrows blood vessels and reduces the availability of oxygen and nutrients to the endometrium. This may reduce the likelihood of embryo implantation by impeding the growth of a robust and responsive endometrium (Sheikhansari et al., 2020).

- *Immunological Determinants*

RIF is attributable to various reasons; however, new research indicates that adequate immune system modulation is essential for endometrial receptivity (Boniface & Esfandiari, 2024). The maternal immune system must sustain a balance between immunological-mediated defense and fetal antigen tolerance during pregnancy to establish an environment amenable to the implantation of the semi-allogeneic embryo without rejection. However, when these factors are upset, it can result in implantation failure.

The endometrial population of natural killer (NK) cells is one of the most crucial immunological factors involved in implantation (Fukui et al., 2015). If the maternal immune tolerance is optimal towards fetal antigens, the development of decidua and the remodelling of vascular connections will proceed properly. RIF patients have been detected with increased cytotoxicity due to uterine NK Cells even though they are key players of angiogenesis (Von Woon et al., 2022). In fertile women, the population of uNK cells was comparatively reduced compared to the infertile group(Kwak-Kim, 2022). Nonetheless, an imbalance in immune cells, including macrophages and T-cells, can set off an inflammatory reaction that could hinder implantation(Zhang et al., 2022). Moreover, autoimmune disorders such as antiphospholipid syndrome (APS), characterized by the immune system attacking the body's own tissues, might worsen the process of implantation by creating an inhospitable uterine environment (Makrigiannakis et al., 2011).

Cytokines are signaling molecules that facilitate immunological responses and are essential in regulating the immune system's function within the endometrium. In implantation failure, a disrupted cytokine balance, specifically an increase in pro-inflammatory cytokines, has been observed(Hortal et al., 2023).

RIF patients often have their Th1/Th2 ratio dysregulated, which is accompanied by an elevation in the IFN-alpha and TNF-beta(Kuroda et al., 2021) .Abnormal Th-17 levels lead to miscarriages. Another group of cells that aids in promoting immune tolerance is Tregs (regulatory T-cells). The imbalance of T-reg cells has resulted in RIF due to increased inflammation and an altered cytokine profile. Treg deficiency results in excessive activation of Th1, Th17, TNF-alpha, and IL-17, which promotes endometrial inflammation and impair trophoblast invasion. Studies have shown that Tregs are essential for proper decidualization and to tolerate fetal antigens(Bellelis et al., 2013). Decidualization is the transformation of endometrial stromal cells into secretory cells, thereby aiding the formation of a protective matrix to support the attachment of the embryo. Decidualized stromal cells protect embryo from oxidative stress, dampen maternal immune response, thereby facilitating invasion(Gellersen &

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Brosens, 2014). Poor endometrial receptivity, elevated inflammatory molecules, and impaired angiogenesis are the consequences of defective decidualization (Murata et al., 2022). Lack of decidualization results in infertility, which is dependent on progesterone. In mice, decreased dendritic cells (DCs) caused decline in the rate of successful implantation(Krey et al., 2008) . In humans, the relationship between DCs, T reg and RIF demand more studies. Researchers studied the NK cell dysfunction and proposed that a hyper-reactive immune system could contribute to embryo rejection(A. et al., 2017) . Successful pregnancy demands an even equilibrium between immune cell activation and suppression; any breach of this balance can result in an unsuccessful implantation. A study showed that the level of anti-inflammatory cytokine was lowered in RIF women. These results imply that poor implantation may be caused by a cytokine imbalance in the endometrial microenvironment (Sharfi, 2013).

- *Endometrial Determinants*

A major cause of RIF is the chronic endometritis, which is indicated by the presence of plasma cells in uterine stroma(Likhachov & Taranovska, 2023). In a study, women having RIF, experienced chronic endometritis at a considerably higher rate than women who had successful pregnancies(Murtinger et al., 2022) . Decreased implantation rates and adverse pregnancy outcomes were associated with ongoing inflammation in the lining of uterus (Klimaszyk et al., 2023) . Earlier, endometrial thickness was regarded as a reliable indicator of endometrial receptivity. In contrast to women with endometrial thickness of 12–14 mm, who exhibited an implantation rate of 43%, a study revealed that patients with an endometrial thickness of less than 7 mm on the day of embryo transfer had a lower implantation rate of 23%(Gingold et al., 2015) . Even after the consideration of maternal age and embryo quality, patients with RIF had a higher prevalence of thin endometrium (<7 mm). These results highlight how crucial it is to maximize thickness of the endometrium for embryo transfer during ART cycles(Tomic et al., 2020) .

Another major cause of RIF is weakened decidualization(Okada et al., 2018). A study that examined the biopsies of endometrium from women with RIF and contrasted them with those from women who had a successful pregnancy, found a strong correlation between decidualization failure and the inadequate expression of progesterone receptors (PR) and insulin-like growth factor (IGF) in endometrial stromal cells(Large & DeMayo, 2012) . The implantation rate was significantly lower (27%) for women with impaired decidualization than for those with normal decidual responses (58%) (Tong et al., 2022) . Furthermore, poor endometrial transformation was found to be correlated with progesterone resistance, resulting in non-receptivity(Zhao et al., 2022).

Endometrial receptivity also depends on the homeobox gene HOXA10(F. Li et al., 2015). Integrin beta-3, a cell adhesion molecule essential for embryo attachment, is directly regulated by it(Zhu et al., 2013). According to research, progesterone and estrogen affect the endometrium's HOXA10 expression, which in turn affects the levels of integrin beta-3 reduced integrin beta-3 results from reduced HOXA10 expression, which hinders embryo-endometrial interactions and increases the risk of implantation failure (Sahar et al., 2019).

RIF is linked to glandular development arrest (GDA) in the endometrium. The normal growth of endometrial glands, which is crucial to support the embryo, which is insufficient in this condition. Implantation is hampered by improper glandular growth. During implantation, markers that modulate the immune response include glycodelin, a glycoprotein generated by endometrial glands. Problems with endometrial receptivity, such as glandular growth arrest, may be reflected in variations in glycodelin expression. When GDA happens, the concentration of cyclin E will be lowered (Kosova et al., 2015).

Endometriosis is a condition in which endometrial-like tissue grows outside the uterus, usually on the pelvic peritoneal layer, fallopian tubes, and ovaries. This can lead to chronic inflammation, dysfunction of the immune system, and structural damages to reproductive organs, eventually declining the fertility potential(Freitag et al., 2020). When comparing the endometrial tissue of women with endometriosis and of controls, the former showed higher levels of pro-inflammatory cytokines, such as TNF-α and IL-1β(Demirel et al., 2015) . A successful implantation requires adhesion molecules like integrins, but these molecules were not expressed due to the inflammatory mediators(Tomassetti et al., 2006) . Inaddition, these patients had markedly delayed or insufficient endometrial decidualization, most likely as a result of the altered immunological and hormonal milieu brought on by endometriosis(Boucher et al., 2022) .

Adenomyosis is a condition in which the endometrial tissue get deposited in the myometrium or other uterine muscle layers. This disease causes alteration in the endometrial receptivity and function, and results in deformed uterine anatomy.Women with adenomyosis manifest aberrant vascularization and a marked reduction in endometrial blood flow in contrast to those with normal uterine architecture (Juárez-Barber et al., 2024).Endometrial biopsies in women having adenomyosis revealed that this change in gene expression resulted in poor decidualization (Teh et al., 2023).Moreover, it was demonstrated that myometrial contractions in adenomyosis interfere with the implantation window, thereby lowering the likelihood of embryo attachment (Mahajan et al., 2018). Also, the uterine fluid had increased concentrations of pro-inflammatory cytokines like TNF-α and IL-6, which may create an immunological environment that is not conducive to implantation (Yu et al., 2023). Another study showed women having both the conditions of adenomyosis and endometriosis have lowest implantation rates compared to individual conditions. A significant disruption of endometrial markers, receptivity, elevated inflammatory molecules and reduced thickness of endometrium were observed in women with the combined conditions (Horton et al., 2019).

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➢ *Anatomical Determinants*

- *Polyp*

Localized overgrowths of the endometrial lining, known as endometrial polyps, can cause the uterus to deform and impede the implantation of embryos. These overgrowths may cause abnormal gene expression thereby disrupting endometrial receptivity and also the proper attachment of embryo. According to a research, 18% of women with RIF undergoing IVF therapy had endometrial polyps. The implantation rates in women with polyps were in a declining pattern(Carvalho et al., 2013). Because polyps in the endometrial cavity alter the secretion of mucin and integrin expression, which can interfere the adhesion processes of embryo and endometrium. It was also demonstrated that the polyps can create an inflammatory environment, as evidenced by elevated levels of TNF-α and IL-6(Ifenatuoha & Okewale, 2022). Cakmak, H., & Taylor, H. S. (2012). Endometrial Polyps and Recurrent Implantation Failure: A Review of Literature. Fertility and Sterility, 98(5), 1179-1184.

- *Fibroids*

Benign neoplasms such as uterine fibroids, or leiomyomas, arise within the uterine muscular tissue (Celik et al., 2022). Fibroids can exert their negative effect on implantation and fertility in various ways depending on whether they are submucosal, intramural, or subserosal. According to a meta-analysis of more than 20 studies, women with submucosal fibroids have 43% lower implantation rates compared to controls (Coughlan et al., 2014). By altering the endometrial architecture, the fibroids affect embryo-endometrial adhesion and remodelling of vascular tissues (Devesa-Peiro et al., 2021). Furthermore, women with fibroids have been found to have greater amounts of inflammatory cytokines including TNF-α and IL-1β in their endometrial tissue.Ubaldi, F. M., et al. (2016). Uterine Fibroids and Recurrent Implantation Failure: A Review of Clinical Evidence and Mechanisms. Human Reproduction Update, 22(5), 563-578.

- *Hydrosalpinx*

Hydrosalpinx is a medical condition characterised by the swelling of the fallopian tube due to the accumulation of fluid. Sexually transmitted infections (STIs) or infections that arise from a previous pelvic inflammatory disease (PID) may result in scarring and obstruction of the fallopian tube. Proteases, prostaglandins, and inflammatory cytokines found in the hydrosalpinx fluid have the potential to harm both the uterine lining and embryos. The fluids that are leaked out from uterine lining can cause toxicity to embryo and hamper endometrial receptivity (Donaghay & Lessey, 2007).

The implantation rate of women with hydrosalpinx was 43% lower in patients with hydrosalpinx than in controls without tubal illness. Elevated levels of pro-inflammatory cytokines, like TNF-α and IL-1β, were detected in the tubal fluid of women with hydrosalpinges, and these cytokines were reported to hinder the process of embryo adhesion to the endometrium (Coughlan et al., 2013). This condition has also been correlated with higher risks of miscarriages and poor embryo quality. To enhance the implantation results in these patients, surgical procedures such as salpingectomy or salpingostomy have been recommended. Omichi, C., et al. (2015). Hydrosalpinx and Recurrent Implantation Failure: Impact of Tubal Disease on ART Outcomes. Journal of Assisted Reproduction and Genetics, 32(2), 153-158.

- *Chromosomal Determinants*

Chromosomal aberrations are more common in RIF women. The production of unbalanced gametes leads to implantation failure, thereby resulting in embryo loss. Male infertility conditions, such as azoospermia or extreme oligozoospermia, can lead to more chromosomal translocations. This can break up sperm DNA, which in turn damages the embryo's DNA. A study revealed that women who had more failed implantation cycles, had more chromosomal abnormalities than women in control IVF groups (Raziel et al., 2002). Researchers in the past said there was no link between the embryos that were transferred and chromosomal issues in the parentsthis is probably because the translocations were balanced. This is because only 2% of RIF patients have anomalies. This points out their need, to be studied in relation to other factors, such as uterine, physical, and immune irregularities (Stern et al., 1999). (Koot et al., 2016) found that RIF patients had lowered endometrial gene expression, leading to issues with cell division. Studies have demonstrated that the best stage for embryo transfer is the blastocyst compared to other cleavage stage embryos (Guerif et al., 2004). Furthermore, the frozen embryos showed more successful rates compared to the fresh ones, but this area is still under debate (Shapiro et al., 2014).

- *Environmental Exposure*

Environmental pollutants such as bisphenol, phthalates, and dioxins are often associated with hormonal disruption and interfere with ovarian steroidogenesis. Heavy metals such as lead, mercury and cadmium can affect oocyte quality. Research has shown the correlation between urinary phthalates and lowered reproductive rates (Ehrlich et al., 2012). Moreover, studies have demonstrated that prolonged exposure to pollutants may cause implantation failure. Endometrial receptivity, the window of implantation, and embryo-endometrial crosstalks can be altered due to exposure to detrimental chemicals. Chemicals like BPA have been recognised for their estrogenic effects since 1936, even though the intricate mechanisms by which they exert such effects remain unclear (Gabrielsen & Tanrikut, 2016). Most of the IVF trials showed that these substances disrupt the function of androgens and estrogens. Studies employing female murine animals revealed that this caused infertility. The implantation rates in mice were decreased upon exposure to environmental pollutants. Research reveals that the incidence of implantation failure rises with higher urine BPA quartiles (Kim et al., 2014). Studies have shown that an enriched environment enhances the maternal exposure and helps in preventing embryo loss (de la Cruz Borthiry et al., 2022).

- *Role of Microbiome in Implantation Failure*

It is believed that a balanced microbiota in the uterus supports a healthy inflammatory environment, improves embryo attachment, and supports a successful pregnancy. However, dysbiosis, or an imbalance in this microbiome, is

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thought to be a factor in lost pregnancy and failure in implantation (Wang et al., 2022). The uterine microbiome is responsible for modulating the balance between pro-inflammatory and anti-inflammatory molecules (Lozano et al., 2023). A number of bacterial species, especially harmful ones including Enterobacteriaceae, Ureaplasma, and Mycoplasma, are linked to persistent inflammation in the reproductive system, which can result in unsuccessful implantation. Studies have reported that a high proportion of Lactobacillus species enhances reproductive outcomes. On the other hand, the population of Streptococcus and Gardnerella results in adverse outcomes (Rokhsartalab Azar et al., 2024).

III. ADVANCEMENTS IN THE TREATMENT FOR RIF

Platelet-Rich Plasma (PRP) which is rich in cytokines, when used as intrauterine infusion has shown to increase successful implantation rates, thereby making it as one of the effective option for RIF(Rageh et al., 2020)&(Elnafarawi et al., 2022). Also studies have revealed that endometrial receptivity can be enhanced by the administration of Peripheral blood mononuclear cells such as B, T-lymphocytes and monocytes in RIF patients. The weakened endometrium can also be strengthened using the G-CSF (Granulocyte Colony-Stimulating Factor), in which they aids in increasing the thickness of endometrium and thereby pregnancy rates. A retrospective study on Chinese population has shown that modulation of immune system and Lymphocyte immunotherapy has significantly elevated the implantation rates, particularly in couples having primary infertility (NCT03267797, 2017). In addition to this, the intrauterine administration of Human chorionic gonadotrophin has improved clinical pregnancy rates in RIF patients (Shihabudeen, 2022)&(Q. Li et al., 2022). Immunotherapies using tacrolimus in RIF patients with elevated Th1/Th2 ratio seem to yield more successful live birth rates compared to controls (Nakagawa et al., 2015). A similar kind of immunotherapy using IVIG (Intra venous immunoglobulin) can be administered to RIF patients who have an abnormal NK cell population and disrupted Th1/Th2 ratio.

Endometrial scratching is one such method shown to increase uterine receptivity by creating injury to the endometrial layer. This seems to be successful for the short term, but this needs to be conducted in larger cohorts, and its safety needs to be ensured in the long run (van Hoogenhuijze et al., 2017). Overexpression of BCL6 is associated with poor endometrial receptivity, which can lead to progesterone resistance, which is a crucial hormone for successful implantation(Summers et al., 2020). Often, women with endometriosis exhibit aberrant expression of BCL6(Goharitaban et al., 2022).(Guo et al., 2018) In his study, he used GnRH agonists that can solve the issues of receptivity and enhanced implantation rates in RIF patients. The ERA of over 238 genes has been published, which can give a precise understanding of endometrial dating(Glujovsky et al., 2023).

IV. CHALLENGES AND FUTURE DIRECTIONS FOR RIF

Earlier, endometrial dating was the primary method for assessing infertility. Afterwards, the studies have demonstrated that dating alone is insufficient to comprehend the complex etiologies of RIF (Sebastian-Leon et al., 2018). Preliminary studies were not sure about the cause of polyp formation, but current research suggests it is due to the hyper-estrogen state. To better understand the causes of thrombophilia, advanced research has been conducted on endometrial immune cells (Bellver et al., 2008)&(Fabregues et al., 2023). The diagnostic criteria for endometritis is still a subject for debate, which refrains from having a proper diagnostic tool. MTHFR (methylenetetrafolate reductase) is an enzyme which is responsible for folate metabolism and DNA methylation. Mutation in this enzyme can affect the vascular tissues and lower blood flow and may hamper endometrial receptivity. It is unclear how MTHFR and RIF are related; while some research points out a connection, women with hereditary thrombophilia can also have RIF. A few studies conclude that it is unrelated, thus, more investigation must be conducted to identify any possible correlations.

Endometrial receptivity can be better diagnosed with the use of the ERA test, biopsy, and ER mapping. Most implant attempts fail if the window period is unspecified. ERA aids in the analysis of the behaviours of over 200 genes that are crucial to the endometrium's receptivity (Fatemi & Popovic-Todorovic, 2013). Gene editing represents the cutting edge method for addressing implantation issues, it is crucial to develop non-invasive methods to immediately assess the transcriptional state of the endometrium. Studies have demonstrated that luteal phase defects (LPDs) will have detrimental effects on implantation, based on the idea that a shorter luteal phase will not allow for the proper attachment of the embryo (Donaghay & Lessey, 2007). This has been a topic of controversy over time, necessitating further studies with larger sample sizes and homogeneous conditions. Most infertility clinics focus on static methods, but time stresses the need for a more personalised approach with non-invasive diagnostic tools. A study shows that women with endometrial injury before implantation have more successful rates, but they do have limitations based on randomized clinical trials with more insights into the inflammatory risks, including maternal age; the time of injury should be uniform to their menstrual cycle (Daya, 2009).

A combined treatment including estrogen/progesterone supplementation, curing of endometrium using G-CSF, aspirin therapy have to be implemented for assessing the long term outcomes (“P78: Influence of Granulocyte Colony-stimulating Factor on Immune Pattern of Endometrium of Patients with Recurrent Implantation Failures in Assisted Reproduction Cycles,” 2019) & (Szekeres-Bartho & Balasch, 2008). The rigorousness of machine learning and artificial intelligence (AI) algorithms for evaluating transcriptomic data can further enhance this understanding. Currently, non-invasive techniques like gene editing and pre-genetic testing are emerging to enhance the rates of implantation. Lately, the

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attention towards the correlation of the endometrial microbiome and RIF is expanding. According to studies, the uterine microbiota can affect both embryo implantation and the receptive nature of the endometrium. Diagnostics using Pre-implantation genetic test and immune modulation are the developing strategies for sorting out this infertility issue.

Pre-implantation genetic testing (PGT) is essential for detecting aneuploidy-related chromosomal abnormalities. Along with next-generation sequencing (NGS), they can improve the successful rates of implantation. (Rubio et al., 2013) have shown that the live birth rate in patients who are evaluated with PGT and the control didn't show any significant difference, but this needs to be verified in a larger sample size. Compared to PGT, single nucleotide polymorphisms seem to be more promising to screen the chromosomes and to sort implantation failures. The potential scopes of stem cell therapy need to be investigated to cure the damaged endometrium. Incorporation of personalised approaches, advancements in AI, sequencing the chromosomal aberrations and improving the reliability of ERA, ER mapping and WOI tests can help people who are undergoing RIF and tackle infertility issues. The reasons for RIF being considered "unexplained" are that the therapeutic options have been identified only for a few etiologies, while many remain unrevealed.

V. CONCLUSION

Recurrent implantation failure is one of the infertility conditions that require personalised approaches. Analysis using SNPs is helpful because it helps in finding the genetic differences linked to uterine receptivity. Looking deeper into the window of implantation, incorporating hormone supplementation therapies and modulating immune functions, we can treat RIF. We need to conduct further research to understand how SNPs contribute to investigating the inflammatory status of the endometrium during the application of the endometrial scratching technique. SNPs will be a promising tool to optimise embryo selection, screen the microbiota essential for the endometrium's receptivity, and reduce the risks associated with thrombophilia. All these combination treatments will help in increasing the successful implantation rates and enable the transition from a trial-and-error method to a precise model.

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